REMARKS

Status

Claims 1-3, 8, 10, 12, 13, 21, 30, 31, 68 and 71 were at issue in this Office Action. The present response does not add or cancel any claims, and accordingly it is claims 1-3, 8, 10, 12, 13, 21, 30, 31, 68 and 71 which are the subject of this response.

The Office Action

In the Office Action mailed March 17, 2009, the Examiner withdrew all previously made rejections. Applicant thanks the Examiner for his thorough consideration of the amendments and remarks previously made and for withdrawal of those rejections.

In the subject Office Action the Examiner has rejected claims 1-3, 8, 10, 13, 30, 31, 68 and 71 under 35 U.S.C. §103 as being unpatentable over U.S. Patent 6,730,471 of Katerkamp. In addition, claims 1-3, 8, 10, 12, 13, 21, 30, 31, 68 and 71 were rejected under 35 U.S.C. §103 as being unpatentable over the Katerkamp '471 patent taken further in view of U.S. Patent 5,652,142 of Barker.

Applicant thanks the Examiner for the further search and for the thorough explanation of the basis of the present rejections.

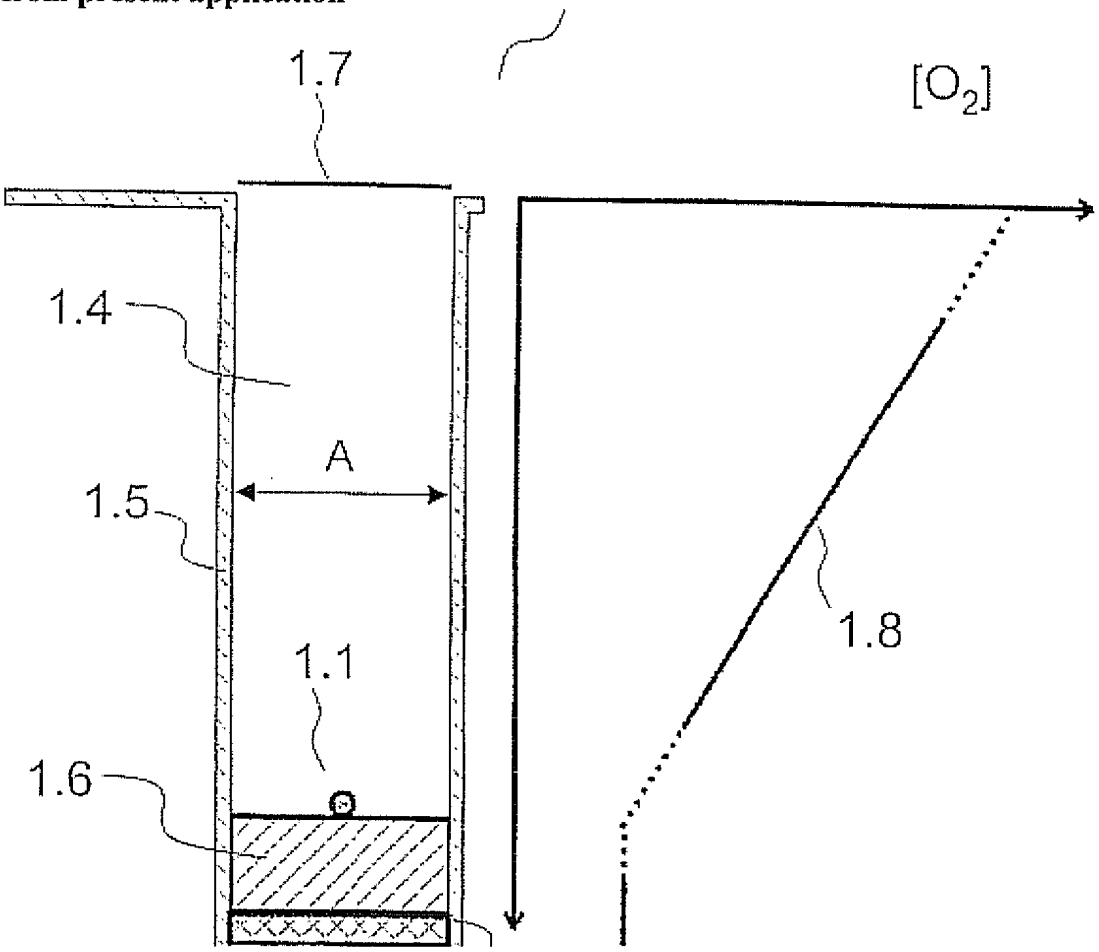
The Present Invention

Before discussing the prior art documents cited, Applicant would like to discuss the present invention in more detail, in particular in relation to diffusion gradients as taught and understood in the context of the present invention.

When a metabolite is transported as a result of diffusion **only**, then the metabolite concentration gradient is a **diffusion gradient**. A diffusion gradient is a gradient in concentration of a substance as a function of distance through a medium; and the movement of

the substance down its concentration gradient is thus called diffusion. Thus, as a matter of principle, when depicting a diffusion gradient of a substance such as oxygen, for example, in a coordinate system, wherein one axis represents the oxygen concentration and the other axis represents the distance from a reference point such as a metabolising particle, the gradient forms a straight line when the medium is placed in a well having a constant cross-section area, see for example Figure 1, from the present patent application, also shown below:

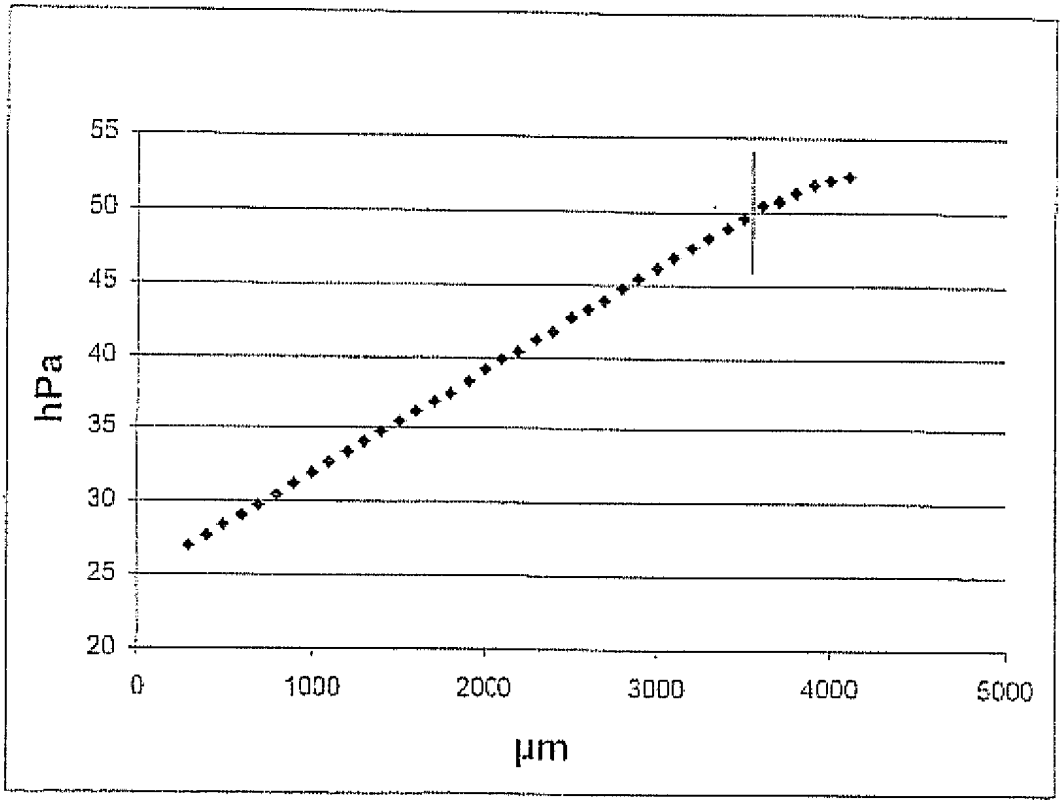
Figure 1 from present application



Due to the linearity, a measure for the oxygen consumption may be established from the slope of the line.

Example 4 of the present application is another example of a diffusion gradient depicted in a coordinate system, wherein the distance is shown at the x-axis and the partial pressure = concentration for gases is shown at the y-axis. Again a straight line is formed, showing that a diffusion gradient has been established **throughout** the medium. The vertical line in Figure 4 shows the interface between medium and open air.

Figure 4 of present application



Thus, before discussing the prior art it is relevant to emphasize that a graphical depiction of a diffusion gradient is a **straight line** in a coordinate system having distance and concentration on the two axes.

Furthermore, it is important to emphasize that the diffusion gradient according to the present invention is established **throughout** the medium.

Rejection – 35 U.S.C. §103

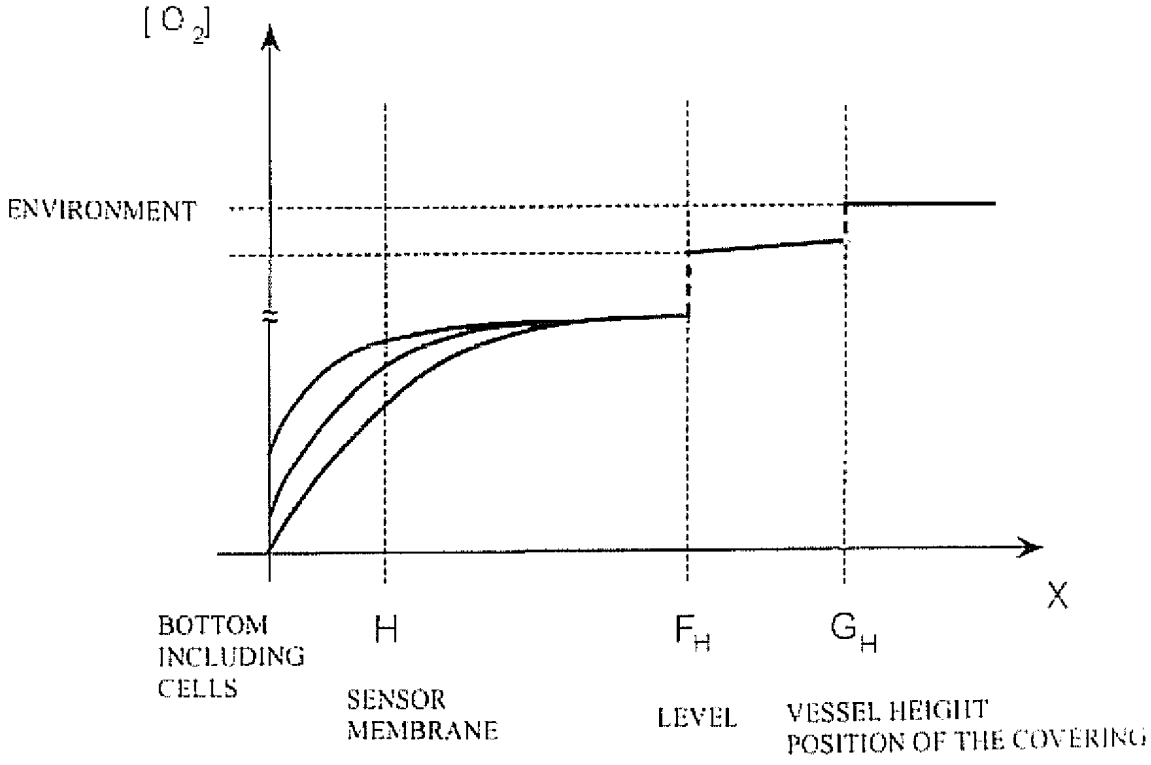
The Examiner refers to Katerkamp et al. (US 6,730,471) and states that Katerkamp "teaches a device … such that an oxygen diffusion gradient is established..:" by referring to column 8, lines 30-35 and Figure 6.

However, column 8, lines 30-35 of Katerkamp states:

> These facts are reproduced in the graph according to Figure 6, and it is intimated that oxygen concentration between the level F_H and vessel height G_H is subjected to a particular gradient of oxygen concentration as well which is elicited by the covering 28 during oxygen consumption caused by metabolic activity.

Thus, this passage of Katerkamp teaches *a particular gradient of oxygen concentration* but does not discuss a diffusion gradient. The section of Katerkamp et al. refers to Figure 6, which is depicted below:

Figure 6 from Katerkamp et al.



Turning to Figure 6, see the above figure copied from Katerkamp et al., it is seen that distance from bottom is shown on the x-axis and oxygen concentration is shown on the y-axis, i.e. the same type of coordinate system as shown in Figure 4 of the present application.

It is clear when studying Figure 6 of Katerkamp et al. that the **oxygen concentration is not a linear function of the distance from the bottom** and throughout the medium. In fact it is seen that the concentration approaches asymptotically towards a specific concentration when the distance approaches F_H, thereafter the concentration makes a jump at F_H and another jump at G_H before reaching the interface between medium and environment.

Furthermore, the y-axis is cut at ≈ further indicating a non-linearity of the concentration gradient.

Katerkamp et al. also includes Figure 2 showing another embodiment of the device according to Katerkamp et al. – however Figure 2 also shows a non-linear function.

Thus, with the basic knowledge that a diffusion gradient would be established as a straight line in a coordinate system as shown in Figure 6 of Katerkamp et al. and seeing that the concentration gradient in Figure 6 is not a straight line, then it is clear that the device according to Katerkamp et al. does not comprise a compartment having:

> a diffusion barrier, wherein said diffusion barrier is arranged around the substantially spherical metabolizing particle to restrict and reduce the diffusive flux of metabolites to and from the particle ... so that a metabolite diffusion gradient is established from the substantially spherical metabolizing particle and throughout the medium in said at least one compartment.

Therefore, contrary to the statement of the Examiner, Katerkamp et al. does NOT teach a culture device such that an oxygen diffusion gradient is established, and in particular there is no

discussion in Katerkamp et al. about a diffusion gradient being established throughout the medium.

Furthermore, the principle of Katerkamp et al. does not work through establishment of an oxygen diffusion gradient, and therefore it is not obvious to start from Katerkamp et al. when discussing obviousness.

It is clear from the discussion of Katerkamp et al., and in particular from Figure 6 as described above, that Katerkamp does not establish a diffusion gradient in accord with the linear diffusion gradient described in the present patent application. Furthermore, the structure of the Katerkamp cell, as described, for example in Figure 5, would not function to provide such a diffusion gradient in accord with the present claims. As noted by the Examiner, the Katerkamp et al. cell of Figure 5 includes a volume of culture medium disposed in a Microwell which is provided with a covering shown at reference numeral 28 (see column 8, lines 19-35). This covering functions to prevent contaminants from entering the cell and to limit drying out of the culture medium. As noted in the specification of Katerkamp et al., the covering is permeable to oxygen. However, nowhere in Katerkamp et al. is it taught that the covering forms a diffusion barrier which, as recited in the claims at issue, functions to restrict and reduce the diffusive flux of metabolites to and from the particle. In contrast, the covering of Katerkamp et al. is a protective, porous body. This is evidenced by the fact that the concentration of oxygen in Katerkamp, as discussed above, does not form any type of linear gradient typical of a diffusion limited process.

By the present amendment, Applicant has amended claim 1 to make clear that it is a "linear metabolite diffusion gradient" which is established through the medium by the diffusion barrier. This element is not shown or suggested in Katerkamp et al. Therefore, in view of the

clarifying remarks above, and the present amendment, Applicant respectfully submits that the claims at issue clearly differentiate over the device and method of Katerkamp et al., and all rejections based thereupon are overcome.

In addition to the foregoing, claims were rejected as being obvious over the teaching of Katerkamp et al. taken further in view of U.S. Patent 5,652,142 of Barker. The Barker patent was cited for its teaching of an insert used in a cell culturing system which may be positionable and repositionable within a culture well so as to allow cells to be grown on both sides of the insert. As such, it was specifically cited for its teaching with regard to embodiments of the present invention wherein an insert may be used for adjusting the dimensions of a culture well. It is notable that the Barker patent does not teach any system or method for establishing any type of diffusion gradient, nor does it show any type of structure which would do so. It is the Examiner's position that combining the culture device of Katerkamp et al. with the cell culture insert device of Barker et al. will approximate Applicant's claimed invention. Applicant respectfully submits that such would not be the case given the general inapplicability of the Katerkamp et al. patent as discussed above, and further in view of the fact that the Barker patent in no way shows or suggests any structure for developing any type of diffusion gradient, and in particular a linear metabolite diffusion gradient as required by the claims at issue. Therefore, all rejections based upon the combination of Katerkamp et al. and Baker et al. are moot.

Conclusion

In view of the foregoing amendment and remarks, Applicant respectfully submits that all rejections are overcome and the application is in condition for allowance. Any questions, comments or suggestions the Examiner may have which would place the application in still better condition for allowance should be directed to the undersigned attorney.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 07-1180.

Dated:

Respectfully submitted,

By _____

Ronald W. Citkowski
Registration No.: 31,005
GIFFORD, KRASS, SPRINKLE, ANDERSON
& CITKOWSKI, P.C.
2701 Troy Center Drive, Suite 330
Post Office Box 7021
Troy, Michigan 48007-7021
(248) 647-6000
(248) 647-5210 (Fax)
Attorney for Applicant